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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,651	01/16/2001	Stefan Kiesewetter	206579	2260

23460 7590 11/19/2003

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,651	KIESEWETTER ET AL.	
	Examin r	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) *15-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,9 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's response filed May 12, 2003 has been considered. Rejections and/or objections not reiterated from the previous office action mailed January 7, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Oath/Declaration

2. Receipt of applicants' properly executed declaration is acknowledged and has been fully entered.

Response to Amendment

3. Newly submitted claims 15-29 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the newly recited claims are directed exclusively to methods of treatment that are patentably distinct from the compounds and methods of making examined in the first Office action on the merits. The newly claimed methods of treatment are related to the previously examined compounds as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the newly recited methods of treatment, drawn

to administering an RNP molecule to induce neovascularization, may be accomplished using other materially different products such as Vascular endothelial growth factor.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 15-29 stand withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments

4. Claims 8, 9, 11, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and is repeated for the reasons of record cited in the Office action mailed January 7, 2003. The instant rejection of record is presently extended to include newly added claims 11 and 14, for the same reasons of record.

Applicants have traversed the instant rejection, which was set forth against applicants' claims drawn to a ribonucleotide protein (RNP) containing any member of the broad family of S100 proteins. Applicants argue that because the specification describes the S100 proteins of the subject ribonucleotide proteins as having two EF hand motifs and a binding site for zinc(II) ions, and have provided functional language stipulating that such S100 proteins are capable of binding

to the RNA part of the ribonucleotide protein (page 5), that the invention should not be so limited to the one S100 actually described in the specification.

This argument is not considered convincing. The test for whether adequate written description exists is whether applicants were considered to be in possession of the invention as claimed at the time of filing. As cited in the previous Office action, such a requirement may be satisfied by adequate description of a representative sample of S100 structures or functions, or a correlation between the two. Since applicants' broad claim language encompasses any protein from the S100 family, and because the family of S100 proteins is considered to include any allele, homologue or variant that shares S100 functionality from any animal species, regardless of whether such an S100 family member is presently cloned or has yet to be described, the mere recitation of a ZN^{++} and an EF hand motif that is the "most common calcium binding motif found in proteins" (Bentley et al., Curr Opin Struct Biol. 2000 Dec;10(6):637-43, cited to rebut applicants arguments, and not constituting a new grounds of rejection) is not considered to provide a sufficient representative sample of structure or function, or a correlation of the two, to convince one of ordinary skill that applicants were in possession of such a large family of proteins. The recitation of these motifs does not provide for adequately description of features that would allow one of skill to envision any S100 family member over another protein having the same ubiquitously expressed motifs.

Applicants also argue that although the specification does not list by name or by sequence any other S100 proteins that are suitable for the present inventive ribonucleotide proteins, there are over 900 journal articles published on S100 proteins, and that the state of the knowledge of the relevant art is such that the number of species needed to be described under the written

description requirement would therefore be low. However, this argument is misdirected, because applicants' invention is not a protein of the S100 family, but is rather a macromolecule comprising any S100 protein complexed with an RNA sequence and a copper ion, and was necessitated because such macromolecule complexes are not well described in the art. Thus, although there is a relative abundance of information about S100 protein family members, applicant has avoided pointing to any particular reference in the art that might allow one of skill to envision any other S100 protein in the context of the claimed invention, that is, as part of the macromolecule complex. The fact that the S100 family has been described to some degree is not considered evidence that one of skill would recognize applicants' possession of any or all such S100 family members complex structure as instantly claimed.

5. Claims 8, 9, 11, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, and is repeated for the reasons of record cited in the Office action mailed January 7, 2003. The instant rejection of record is presently extended to include newly added claims 11 and 14, for the same reasons of record.

Applicants have traversed the rejection of record, which set forth that the specification teaches making only one specific ribonucleotide protein, and is not enabled for making and using ternary complexes comprising any S100 protein family member with the RNA of SEQ ID NO: 2

and a copper ion. Applicants argue that the method of isolating and purifying the present RNPS can be applied to other ribonucleotide proteins other than the S100 family member of SEQ ID NO: 1. Applicants assert that one of ordinary skill in the art would be able to identify the other members of the S100 family that (i) have two EF hand motifs and a zinc(II) ion binding site and (ii) can bind to a RNA molecule of the subject ribonucleotide proteins. Applicants argue that it would require one of ordinary skill in the art only routine experimentation to determine other S100 proteins that fall within the scope of the claims. Applicants assert that one could do this by performing a binding assay to determine which proteins bind to the oligonucleotide of SEQ ID NO: 3, and that any proteins that bind could be sequenced to determine if any have two EF hand motifs and a zinc(II) ion binding site. The GenBank Database could then be searched for the sequences of the proteins having two EF hand motifs and a zinc(II) ion binding site to determine if it is a known S100 family member.

This is not considered convincing. A primary consideration in the analysis of enablement as set forth in the previous Office action is the unpredictability of the art. It is well known to those of ordinary skill that polynucleotide interactions with proteins that don't normally bind DNA or RNA such as the instant S100 type proteins (See Donato et al., Int J Biochem Cell Biol. 2001 Jul;33(7):637-68., enclosed to rebut applicants arguments and not constituting a new grounds of rejection) do so in a random fashion; such interactions must be experimentally determined. One of skill would understand that one could not predict in the absence of experimentation whether a given polynucleotide would bind to any protein at all. In fact, these unpredictable interactions of polynucleotides with proteins are one the major hurdles confronting the use of small nucleotides such as antisense oligos as therapeutic molecules. One of skill in the

art would consider running an assay to find other S100 proteins that bind a specific sequence of polynucleotide to be an unpredictable venture, particularly in view of the fact that no other examples of nucleotide/S100 binding have been found by the examiner or cited by applicants. Thus, although such an assay could be run, there is no assurance that a polynucleotide so tested will result in binding to any protein, let alone a protein of S100 relation. Such results are thus considered to be unpredictable, and would necessarily cause one of skill to engage in undue trial and error experimentation in order to determine whether such interactions even exist. For these reasons, the rejection of record is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8, 9, 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8, 9, and 11-14 refer alternately to "RNP" and "RPN" to refer to the metal-containing ribonucleotide protein. The specification preferentially uses the term "RNP" to refer to said protein. While it is presumed that applicant is using both of these terms to refer to the same molecule, such alternate references render the claim language indefinite, since it is not clear what is being referred to by such terms.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claim 14 is drawn to an RPN complex or molecular-biological equivalents and/or fragments and/or derivatives thereof.

Applicants' specification does not point to any molecular-biological equivalents and/or fragments and/or derivatives of the claimed composition. Furthermore, the only structural information about one aspect of the claimed macromolecule is that the molecule have an EF hand and a Zn binding domain. As discussed above, such a disclosure, when taken in light of the prior art which is silent as to any other examples of a complex of any member of the S100 family

with a polynucleotide and a copper ion, would not persuade one of skill in the art that applicants were in possession of a complex of any or all members of the S100 family with a polynucleotide and a copper ion. Accordingly, neither is applicant considered to be in possession of the more broadly recited "equivalents" as set forth in claim 14.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD